NIH Blueprint for Neuroscience Research

The NIH Office of the Director and these NIH Institutes and Centers participate in the NIH Blueprint for Neuroscience Research:

- NCCAM
- NCRR
- NEI
- NIA
- NIAAA
- NIBIB
- NICHD
- NIDA
- NIDCD
- NIDCR
- NIEHS
- NIGMS
- NIMH
- NINDS
- NINR
- OBSSR

What is the NIH Blueprint for Neuroscience Research?

The Blueprint is a framework to enhance cooperative activities among the NIH Office of the Director and the NIH Institutes and Centers that support research on the nervous system. By pooling resources and expertise, the Blueprint takes advantage of economies of scale, confronts challenges too large for any single Institute or Center, and develops research tools and infrastructure that serve the entire neuroscience community. Best practices developed at a single Institute or Center are implemented more widely, planning is coordinated at the early concept stage, resources established by one Institute or Center are opened to neuroscientists supported by others, and new working groups can focus on broad disease mechanisms and cross-cutting scientific issues.

How does the Blueprint affect the way the NIH does business?

Each Institute and Center continues to carry out the basic, disease-specific, and life course-specific research unique to its mission. Just as the NIH Roadmap for Medical Research addresses roadblocks that hamper progress across all of medical science, the Blueprint selectively takes on challenges in neuroscience that are best met collectively.

How will the Blueprint affect people's health?

Nervous system disorders take many forms: mental disorders, such as schizophrenia, depression, and obsessive compulsive disorder; neurological diseases, such as stroke, traumatic brain injury, epilepsy, Parkinson's disease, and multiple sclerosis; degenerative dementias of aging, such as Alzheimer's disease and vascular dementia; developmental disorders, such as autism, mental retardation, and attention deficit disorder; inherited and acquired sensory disorders, including visual and hearing loss; chronic pain conditions; alcohol dependence; and drug addiction. Many of these diseases share mechanisms. While the Blueprint does not target individual disorders, the tools, resources, and infrastructure created through the Blueprint have the potential to accelerate research for all of them, which in turn will lead to advances in prevention and treatment.

What are examples of recent Blueprint activities?

NIH Neuroscience Microarray Consortium, a group of four state-of-the-art facilities that allows grantees from all Blueprint Institutes or Centers access to microarray platforms, training, data analysis, and data sharing via an online database.

GENSAT (Gene Expression Nervous System ATlas), a large-scale project to map the expression of thousands of genes in the mouse central nervous system.

NIH Toolbox for Assessment of Neurological and Behavioral Function, a project to develop a set of integrated assessment tools for measuring cognitive, emotional, motor, and sensory health that will be appropriate for diverse populations, settings, and study types.

Recombinase-Expressing Mouse Lines, several grants to develop mouse lines for the study of gene function in distinct cell types or to plot the temporal / spatial patterns of gene expression.

Mouse Archiving, an initiative that supports the unrestricted distribution of genetic mouse models and makes them available to the neuroscience community for further research, development, and application via the Mutant Mouse Regional Resource Centers (MMRRC).

How will the Blueprint develop in the future?

The Blueprint welcomes suggestions from the scientific, clinical, and patient communities for initiatives that will advance the progress of neuroscience research and benefit the neuroscience community. Upcoming initiatives will focus on neurodevelopment (FY2008) and neuroplasticity (FY2009). Contact us by e-mail at blueprint@mail.nih.gov. Workshop summaries, requests for information, new developments, and specific initiatives are posted at www.neuroscienceblueprint.nih.gov.

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GENSAT

GENSAT (Gene Expression Nervous System ATlas) is a large-scale project that plans to map the expression of thousands of genes in the developing and adult mouse central nervous system (CNS). The project involves creation of transgenic mouse lines that express a bacterial artificial chromosome (BAC) containing the gene of interest and an enhanced green fluorescent protein (EGFP) reporter to reveal the pattern of gene expression. A prescreen component is included that utilizes traditional radiometric *in situ* hybridization to give a broad picture of CNS gene expression of candidate genes. Both approaches have created gene expression atlases for mouse brain and spinal cord tissue at three developmental stages and in adulthood.

To date, over 600 transgenic BAC-EGFP reporter mice have been generated to allow the exquisite mapping of gene expression at the cellular level and to provide details of cellular morphology. Recently, twelve fully characterized BAC-CRE recombinase driver lines have been created to serve as tools for cell-specific genetic manipulations in select neuronal populations in the brain and spinal cord. Candidate genes are selected by an NIH-assembled advisory committee using bioinformatics approaches, in addition to suggestions solicited from the neuroscience community.

The gene expression data and mouse brain images are available to the public in online, searchable databases (see below). Future GENSAT studies will include the continued generation of new BAC-EGFP and BAC-CRE recombinase transgenic mouse lines, improved mapping of the GENSAT data, and the possible expansion of GENSAT to include analyses of visual, auditory, and pain pathways.

Since the BAC mouse lines are powerful tools for pursuing other types of experiments in identified cells, GENSAT distributes the mouse strains generated for the project via the Mutant Mouse Regional Resource Centers (MMRRCs). More than 200 BAC mouse lines have been placed in the MMRRC repositories since the beginning of the project and are available for a small fee.

Resources:

NCBI GENSAT Database www.ncbi.nlm.nih.gov/projects/gensat
BAC Transgenic Mouse GENSAT Database www.gensat.org/index.html
In Situ Hybridization GENSAT Database www.stjudebgem.org/web/mainPage/mainPage.php
Mutant Mouse Regional Resource Centers www.mmrrc.org
(select major collection: GENSAT)
Submit nominations for gene review and analysis to info@ncbi.nlm.nih.gov.

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GENSAT is a contract funded by the Institutes and Centers that comprise the NIH Blueprint for Neuroscience Research.

The Mutant Mouse Regional Resource Centers contract is supported by the National Center for Research Resources at www.ncrr.nih.gov with additional funding from the other Institutes and Centers that comprise the NIH Blueprint for Neuroscience Research.

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NIH Neuroscience Microarray Consortium

The NIH Neuroscience Microarray Consortium is a group of four facilities chosen for their outstanding resources and their diverse range of microarray platforms. The Consortium gives NIH-funded neuroscience researchers cost-effective access to state-of-the-art microarray technology for gene expression profiling and SNP genotyping in diverse model organisms. The goal of the initiative is to promote basic and translational research by producing and sharing high-quality genomic data.

The National Institute of Neurological Disorders and Stroke (NINDS) and the National Institute of Mental Health (NIMH) originally established the Consortium, and the Blueprint initiative began contributing funds in FY2005. This gives grantees from all Blueprint Institutes and Centers access to the Consortium resources on a fee-for-service basis.

Resources:

Consortium Centers http://arrayconsortium.tgen.org

- Duke University, Durham, NC
- Translational Genomics Research Institute (TGen), Phoenix, AZ
- University of California, Los Angeles, CA
- Yale University, New Haven, CT

Microarray Platforms

- cDNA
- Oligonucleotide
- Affymetrix
- Agilent
- Illumina

Other Services

- Laser Capture Microdissection
- Experimental design assistance prior to project submission
- Data analysis support via statistical software packages and online and on-site training
- Data sharing via the Consortium online databases
- Education and training that emphasizes experimental design, technical procedures, and data analysis techniques specific to neuroscience research
- Manuscript assistance and consultation

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The NIH Neuroscience Microarray Consortium (http://arrayconsortium.tgen.org) is funded by the Institutes and Centers that comprise the NIH Blueprint for Neuroscience Research.

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Experimental Mouse Lines

Development of Recombinase-Expressing ("Driver") Mouse Lines for Studying the Nervous System

The use of experimental mice is widely recognized as a critical component of biomedical research, including studies of the development and function of the nervous system. The grants in this program support the design, creation, and characterization of recombinase-expressing ("driver") C57B1/6 mouse lines, which can be used to study gene functions in distinct cell types and temporal or spatial patterns in the nervous system.

Through cooperative agreements with multiple investigators, 100 or more novel recombinase-expressing mice will become available in the next several years along with characterization data detailing the recombinase-expression profile for each mouse line.

Details on the specific lines generated through this effort, anticipated availability dates, and distribution information will be posted on the NIH Blueprint for Neuroscience Research website (www.neurosciencebluprint.nih.gov) as they become available.

Mouse Archiving and Central Distribution

Supplemental funds have been provided to two mouse repositories supported by the National Center for Research Resources (NCRR) to archive existing mouse lines of interest to the neuroscience community and to provide central distribution services and quality control. Approximately 220 mouse lines will be deposited in the Mutant Mouse Regional Resource Centers (MMRRCs) at the University of California at Davis and the University of Missouri/Harlan.

This Blueprint funding ensures that experimental mice developed with NIH support will be made readily available in a timely fashion to the research community for further research, development, and application. This furthers the research enterprise, increases knowledge, and accelerates the development of products to benefit the public.

Resources:

Mutant Mouse Regional Resource Centers www.mmrrc.org

NIH Policy on Sharing of Model Organisms for Biomedical Research
www.nih.gov/science/models/sharingpolicy.html

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The grants supporting the Development of Recombinase-Expressing ("Driver") Mouse Lines for Studying the Nervous System are funded by the Institutes and Centers that comprise the NIH Blueprint for Neuroscience Research.

The Mutant Mouse Regional Resource Centers is a contract supported by the NCRR (www.ncrr.nih.gov) with additional funding from the other Institutes and Centers that comprise the NIH Blueprint for Neuroscience Research.

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Neuroimaging

New Ways to Image Neural Activity

Neuroimaging technologies, such as EEG, MEG, and fMRI, allow us to observe brain functions. To date, however, the imaging techniques that are most commonly used to study neural activation during particular behaviors have been invasive (via the insertion of electrodes or the injection of radioactive tracers), constraining (such as the MRI chamber), or limited in their spatial and temporal resolution (for example, an EEG report is specific about time, but vague about location).

Six grants have been awarded to support the development of new ways to image the brain that are non-invasive, non-constraining, and can capture the rapid neural activation reflected in electrophysiological signals such as action potentials or local field potentials. These new imaging techniques will allow us to view neural activity simultaneously in space and time with high accuracy, making them valuable for measuring the neural underpinnings of behavior.

Clearinghouse for Neuroimaging Software and Data

Many neuroimaging tools and databases are underutilized because they are not user-friendly and there is no independent source of advice about these resources. This contract will establish an Internet-based Clearinghouse for use by the neuroscience community. Information about neuroimaging resources, including tools and databases, will be gathered and evaluated with respect to usage, interoperability, features, quality of documentation and support, and user satisfaction. Forums will encourage interaction between the user and the associated technology developers. Ongoing opportunities will be provided for public comment to guide the development of tools and resources and to enhance their use by the neuroimaging research community. The initial focus of the Clearinghouse is on tools, techniques, and resources for fMRI and directly related structural MRI.

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National Institutes of Health

New Ways to Image Neural Activity and the Clearinghouse for Neuroimaging Software and Data are funded by the Institutes and Centers that comprise the NIH Blueprint for Neuroscience Research.

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NIH Toolbox for Assessment of Neurological and Behavioral Function

Many studies collect data on aspects of neural function, such as cognition, sensation, movement, or emotion, but there is little uniformity among the measures used to capture these constructs. The use of non-standardized assessment tools makes it problematic to compile and compare data across multiple studies. There is a need for concise assessment tools that can be used across diverse study designs and populations.

The goal of the NIH Toolbox project is to develop a set of neurological and behavioral measures that use state-of-the art psychometric research and novel testing methods, which will be useful to researchers in a variety of settings. The end result of the project will be a set of integrated assessment tools for measuring cognitive, emotional, motor, and sensory health with enough flexibility to be appropriate for diverse populations, settings, and study types, such as:

- large longitudinal and epidemiologic studies; and
- prevention or intervention trials.

By using the tools in the NIH Toolbox to measure neurological and behavioral function, investigators will ensure the maximum use of data from large, expensive, long-term studies. The availability of consistent, uniform data will increase the yield from these types of studies by allowing a greater number of research questions relating to neurological and behavioral health to be asked and answered. By creating assessment tools that can be modified or improved in the future, the architects of the Toolbox will ensure that this project is a valuable resource for NIH and the entire neuroscience community.

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The NIH Toolbox for Assessment of Neurological and Behavioral Function is a contract funded by the Institutes and Centers that comprise the NIH Blueprint for Neuroscience Research. For more information about the Toolbox, which is operated by the Evanston Northwestern Healthcare Research Institute (Richard Gershon, Ph.D., Principal Investigator), please visit www.nihtoolbox.org.

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Course Development in the Neurobiology of Disease

This initiative supports the creation or the significant expansion of courses for neuroscience graduate students. "Neurobiology of disease" refers to basic genetic, molecular, and cellular mechanisms that underlie a wide range of neurological and neuropsychiatric diseases and disorders. The courses are designed to foster an understanding of the links between basic science, disease-oriented research, and translational research. The courses offer a foundation of knowledge in critical areas of basic and clinical neuroscience.

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Twelve institutions received grants to develop courses in FY2005 and 2006. Below is a list of the twelve grantees with contact information and links to websites (if available) that offer access to the developed curriculum. These sites offer PowerPoint presentations, videos of patient interviews, links to journal articles, links to disorder related resources such as support organizations and voluntary groups, webcasts of lecture presentations, syllabi, and additional course materials.

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Course Development in the Neurobiology of Disease *(continued)*

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The grants supporting Course Development in the Neurobiology of Disease are funded by the Institutes and Centers that comprise the NIH Blueprint for Neuroscience Research.

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Neurodevelopment Activities

In FY2008, Blueprint funding initiatives are focused on providing tools and resources to advance the field of neurodevelopment. These projects are the result of a team of 32 researchers from diverse areas of investigation who convened at the National Institutes of Health (NIH) to discuss cross-cutting challenges in neurodevelopmental research that might benefit most from Blueprint funding. This team put forward specific recommendations for action; of these, the following initiatives were approved for funding and are in various stages of progress.

Gene Expression in Developing Non-Human Primate Brain

This program addresses the need for a detailed, localized map of gene expression in the developing nervous system. Although the long-term goal is to obtain detailed and searchable maps of gene expression in human brain, using currently available techniques is both premature and cost-prohibitive. A tractable alternative is to pursue pilot studies in specific brain regions in developing, non-human primates. This pilot project focuses on detailing gene expression in the rhesus macaque nervous system at multiple stages of neural development. The accumulated data will be integrated into a publicly available, digital brain atlas and accompanied by informatics tools to search and analyze the data.

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Tools and Techniques for Elucidating and Manipulating Neural Circuit Development

Neural circuit development is a process that occurs during prenatal development and continues into adolescence. It begins with axon and dendrite formation in the embryonic brain, and continues through axon guidance and pathfinding, myelination, synapse formation, and synapse pruning from the prenatal period to the teenage years. Understanding how neural circuits take shape in space and time is essential in order to understand how the normal brain functions and how abnormal development causes disorders of disease, behavior, and personality. Projects supported by this initiative are focused on developing, creating, and distributing new, higher resolution methods for studying the assembly of neural circuits.

This research will yield improved tools and technologies to help identify key genetic, molecular, and cellular transitions between developmental stages of circuit formation.

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Neurodevelopment Activities *(continued)*

Creating Antibodies for Research in Neurodevelopment

Improving the quantities, quality, and distribution of monoclonal antibodies useful for studying neural development is a clear priority for advancing discoveries in the neurosciences. To that end, the Blueprint Resource Antibody Initiative for Neurodevelopment (BRAINdev) has provided funds to create, validate, and distribute approximately 150 monoclonal antibodies over a three year period. These antibodies will be validated in multiple model systems and made readily available to the community via the Center for Evaluation of Neurodevelopmental Antibodies (CENA). Access to these well-characterized antibodies, generated to recognize key molecules in neural development, will advance research in neuroscience across model systems.

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The grants that support Gene Expression in Developing Non-Human Primate Brain, Tools and Techniques for Elucidating and Manipulating Neural Circuit Development, and BRAINdev are funded by the Institutes and Centers that comprise the NIH Blueprint for Neuroscience Research.

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Blueprint and Blueprint-Affiliated Informatics Activities

Blueprint Informatics

Blueprint Informatics Team (BIT)

The BIT has three overall objectives: 1) to accelerate the use of computational approaches in the neurosciences by advancing informatics research, 2) to increase the value of informatics research by encouraging communication, collaboration, and coordination among the Blueprint Institutes and Centers, and 3) to provide a collective neuroscience voice and unified leadership for informatics activities across NIH and within the wider neuroscience research community. The BIT functions as a common platform for hosting discussions about the overarching area of informatics and serves as an integrating force across all informatics initiatives, whether they are Blueprint, Blueprint-affiliated, or otherwise.

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Neuroscience Information Framework (NIF)

The Blueprint launched the NIF in FY2005 to build an Internet-based repository of neuroscience-related material for the research community. The NIF combines resources of the Blueprint ICs and the Society for Neuroscience (SFN) to provide access to information about neuroscience resources for researchers, including website content, reports of national and international research activities, reagents, biological materials, and databases-all searchable by content and usage. NIF invites registered users to catalog their electronic and non-electronic neuroscience research resources at www.neurogateway.org

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Blueprint and Blueprint-Affiliated Informatics Activities *(continued)*

Blueprint-Affiliated Informatics

Biomedical Informatics Research Network (BIRN)

The goal of the BIRN is to develop an infrastructure that allows researchers to share data, both for limited collaborations inside a defined research group and also among the research community at large. Most of the basic BIRN infrastructure has been developed at the University of California, San Diego under a Coordinating Center award. Three large testbed projects, all of which involve neuroinformatics research, have been funded to insure that the data-sharing infrastructure is responsive to the needs of biomedical investigators. These projects are focused on structural MRI imaging, functional MRI imaging, and new techniques for merging and blending imaging technologies and image resolutions. The tools developed with support from this project are freely available to the biomedical community via the BIRN website at www.nbirn.net

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Blueprint Informatics Funding Opportunity Announcements (FOAs)

Developed under BIT to take advantage of the BIRN infrastructure already in place, two Blueprint-affiliated FOAs have recently been announced.

Tool and Data Sharing (PAR-07-426 grants.nih.gov/grants/guide/pa-files/PAR-07-426.html) asks researchers to apply for funds to bring either their data analysis tools or their data into the BIRN infrastructure for the research community. The BIRN infrastructure is unique in that it allows multiple data analysis tools to be compared against each other in a common environment using real data. The infrastructure also provides a convenient way for researchers to store and share their data.

Data Ontologies (PAR-07-425 grants.nih.gov/grants/guide/pa-files/PAR-07-425.html) tackles a deeper problem of research data sharing – how to match the meanings of words when their usage varies among data sets. This grant will support research to create an ontology using controlled vocabularies for two datasets in a specific research area. Once the ontology is created, it will be shared within the field. Contacts from individual Institutes and Centers are listed in each FOA.

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Active Programs

Biomarkers for Neurodegeneration
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BRAINdev
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Mouse Archiving and Central Distribution
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Neuroscience Microarray Consortium
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Active Programs *(continued)*

New Ways To Image Neural Activity
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NIH Toolbox for Assessment of Neurological and Behavioral Function
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Short Term Interdisciplinary Career Enhancement Awards for Neurodegeneration Research
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Tools and Techniques for Elucidating and Manipulating Neural Circuit Development
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Training in Computational Neuroscience
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